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ARTICLE

Bounded integer model-based analysis of psoriasis area and severity index in patients with moderate-to-severe plaque psoriasis receiving BI 730357

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Abstract

BI 730357 is investigated as an oral treatment of plaque psoriasis. We analyzed the impact of three dosage regimens on the Psoriasis Area and Severity Index (PASI) response with modeling based on phase I and II data from 109 healthy subjects and 274 patients with moderate-to-severe plaque psoriasis. The pharmacokinetics (PK) was characterized by a two-compartment model with dual absorption paths and a first-order elimination. Higher baseline C-reactive protein was associated with lower clearance and patients generally had lower clearance compared with healthy subjects. A bounded integer PK/pharmacodynamic model characterized the effect on the observed PASI. The maximum drug effect was largest for patients with no prior biologic use, smaller for patients with prior use of non-interleukin-17 inhibitors, and smallest for patients with prior interleukin-17 inhibitor use. The models allowed robust simulation of large patient populations, predicting a plateau in PASI outcomes for BI 730357 exposure above 2000 nmol/L.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

There are no published retinoic acid-related orphan receptor gamma inhibitor population pharmacokinetic (PK) and PK/pharmacodynamic (PD) models based on clinical data.

WHAT QUESTION DID THIS STUDY ADDRESS?

Which Psoriasis Area and Severity Index (PASI) outcomes are predicted for different BI 730357 dosage regimens through population PK and PK/PD modeling and simulation?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

A bounded integer PK/PD model with improved numerical stability successfully characterized the BI 730357 effect on the observed PASI in patients with

[Correction added on 17 May 2023, after first online publication: The author name "Elodie Plan" has been changed to "Elodie L. Plan" .]

moderate-to-severe plaque psoriasis. Model simulations predicted an exposure-response plateau in the relative change from baseline PASI.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

Application of a PK/PD model with bounded integer structure to simulate score data with boundaries can contribute to model-informed drug development.

INTRODUCTION

The retinoic acid-related orphan receptor gamma (RORγ) has been proposed as the master regulator of the interleukin (IL) IL-17/IL-23 pathway involved in the pathophysiology of immune-mediated disease, such as psoriasis, psoriatic arthritis, and inflammatory bowel disease.[1–6] BI 730357 is a competitive antagonist to RORγ and is investigated as an oral treatment of plaque psoriasis. Plaque psoriasis is a chronic inflammatory skin disease characterized by red plaques covered in silvery scales that cause itching, stinging, bleeding, and pain.[7,8] Patients with plaque psoriasis can experience great psychosocial burden and have an increased risk of cardiovascular disease, diabetes, and depression.[7–9]

Clinical investigations of BI 730357 as a potential treatment of plaque psoriasis include phase I studies enrolling healthy subjects and a phase II study enrolling patients with moderate-to-severe plaque psoriasis. Characterization of dose-exposure and exposure-response profiles, including the interindividual variability, is of interest to bridge between once daily and twice daily dosage regimens. Furthermore, an exposure-response analysis can maximize the power of detection and quantification of clinical efficacy.

Patients' response to treatment was evaluated by the composite scale Psoriasis Area and Severity Index (PASI).[10] Modeling of composite scales often treat the end point as either a continuous variable, making assumptions that violate the integer nature of the data, or as an ordered categorical variable, which often involves the estimation of many parameters, especially for scales with a large number of possible categories.[11] In an effort to respect the discrete and bounded nature of the data in a parsimonious way, the bounded integer model was proposed.[11] The bounded integer model assumes a latent grid defined by quantiles of a standard normal distribution where each subject's probability for a certain score is a function of its mean and variance over time on the latent scale.[12]

We used population pharmacokinetic (PK) and bounded integer PK/pharmacodynamic (PK/PD) modeling to characterize the relationship between BI 730357 exposure and response in patients with psoriasis and simulate the efficacy after administration of BI 730357 to the target patient population in study replicates. Our aims were to (1) characterize BI 730357 PK properties following oral administration, (2) investigate the relationship between BI 730357 concentration and PASI response, and (3) predict the expected PASI outcome for three BI 730357 dosage regimens.

METHODS

Population PK model development was initiated using data from healthy subjects. With stepwise availability of interim data from patients, the population PK model was updated and the PK/PD model was developed, and both models were updated as final data emerged. Only details related to the development of the final models using the final analysis datasets are presented.

Clinical data collection

The population PK analysis used data from three phase I studies in healthy subjects (1407-0002, 1407-0032, and 1407-0033) and one phase II study in patients with moderate-to-severe plaque psoriasis (1407-0030). The PK/PD analyses were based on patient data from study 1407-0030, whose main clinical end points included PASI, static physician global assessments (sPGA, data not shown), and β-defensin (data not shown).

The study protocols were approved by the institutional review board or ethics committee at each study site and the studies were conducted in accordance with Good Clinical Practice guidelines and adhered to the Declaration of Helsinki. All subjects provided written informed consent before any study procedures were undertaken. A summary of the clinical data included in the analyses is provided in Table 1.

Placebo data, predose PK samples, and postdose PK samples below the limit of quantification (4.68% of the postdose PK samples) were excluded from the population PK analysis. Records for one subject which contained errors, one record which corresponded to a suspected

TABLE 1 Summary of clinical studies and analysis data.

Study	Population	Dose	Data
1407-0032 phase I	Healthy subjects	50 mg, 100 mg, 200 mg single oral dose under fasted condition	42 subjects with 1191 BI 730357 plasma concentrations Plasma samples obtained at 2 h before dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, 34, 47, 71, 119, 167 h after dose
1407-0033 phase I	Healthy male subjects	50 mg single oral dose with 100 µg intravenous microtracer under fasted condition	6 subjects with 145 BI 730357 plasma concentrations Plasma samples obtained at 2 h before the oral dose and at 0, 1, 1.25, 1.33, 1.42, 1.5, 1.75, 2, 2.5, 3.5, 4, 5, 7, 11, 12, 24, 72, 120, 168 h after the oral dose
1407-0002 phase Ib	Healthy male subjects		61 subjects with 2286 BI 730357 plasma concentrations
		25 mg, 50 mg, 100 mg once daily orally for 14 days under fasted condition 50 mg once daily for 14 days under fed condition	Plasma samples obtained at 0.5 h before dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 23.5 h after the first and the last dose and at 47.5, 71.5, 168 h after the last dose Trough samples obtained on days 3, 7, 10, 11, 12, 13, 14 at 23.5 h after dose
		200 mg once daily orally for 28 days under fasted condition 200 mg, 400 mg once daily for 28 days under fed condition	Plasma samples obtained at 0.5 h before dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 23.5 h after the first dose and at 1, 2, 3, 4, 6, 24, 168 h after the last dose Trough samples obtained on days 3, at 7, 8, 11, 12, 13, 14, 15, 16, 17, 21, 24, 28 at 23.5 h after dose
1407-0030 phase II	Patients with moderate-to-severe plaque psoriasis		274 patients with 1554 PASI assessments PASI assessed at screening on 28 to 7 days before dose and on days 1, 8, 15, 29, 57, 85, 113, 141, 169, 197 after dose 244 patients with 4064 BI 730357 plasma concentrations
Part 1		25 mg, 50 mg, 100 mg, 200 mg once daily orally for 24 weeks[a] under fasted condition	Plasma samples obtained on days 1, 29, 85 at 0.25, 0.5, 1, 2, 3 h after dose Trough samples obtained pre-dose on days 4, 8, 15, 57, 113, 141, 169, 197
Part 2		200 mg twice daily, 400 mg once daily orally for 12 weeks under fed condition	Plasma samples obtained on days 1, 15, 84 at intervals 0.25–1, 1.5–2.25, 2.75–3.5 h after the morning dose Trough samples obtained at 90–5 min before the morning dose on days 1, 4, 8, 15, 29, 57, 84 In a sub-group, plasma samples obtained on day 1 and 84 at 0.5, 1, 2, 3, 5, 8, 24 h (within 30 min before the next dose), 48, 72 h after the morning dose

Abbreviation: PASI, Psoriasis Area and Severity Index.

[a]Only data from 12 weeks of treatment were analyzed, in accordance with the analysis plan.

swapped PK sample, and records for subjects in study 1407-0032 who were administered coarse milled or un-milled intended commercial BI 730357 formulation were also excluded from the population PK analysis.

The clinical assessment tool PASI was used to evaluate patients' response to treatment. Briefly, assessments of the extent of skin area affected were combined with the severity of erythema, thickness, and scaling into a PASI score ranging from 0 to 72.[10] PASI assessments from the screening phase were excluded from the PK/PD analysis.

Population pharmacokinetic modeling

For the BI 730357 population PK model development, first-order, parallel and sequential zero- and first-order

absorption models were evaluated, besides one-, two-, and three-compartment disposition models with first-order elimination from the central compartment. Absorption was further evaluated by a parallel slow absorption path with a delay described by a long absorption lag time, and a brief absorption lag time added to the main absorption path.

Interindividual variability (IIV) was evaluated on all relevant PK parameters. IIV was included in an exponential manner for parameters which have a lower bound of zero and in an additive manner for parameters which can take on both negative and positive values, such as parameters on the logit scale. Additive, proportional, and additive plus proportional error models were explored for residual unexplained variability (RUV). IIV on RUV[13] and scaling of RUV using the lower limit of quantification were also attempted. Specification of RUV by studies and/or diet status was considered for more accurate characterization of RUV and better attribution of sources of variability.

Covariate-parameter relationships were tested using the stepwise covariate model building procedure[14] with $p = 0.01$ for forward selection and $p = 0.001$ for backward elimination in Perl-speaks-NONMEM,[15] including the algorithm with adaptive scope reduction.[16] Continuous covariates were tested using a power model and a linear model for logit transformed parameters and categorical covariates as a fractional difference to the most common category. The tested covariate-parameter relationships are listed in Table S1.

Population pharmacokinetic/pharmacodynamic modeling

A bounded integer model[11] implemented with improved numerical stability[12] was used to describe the PASI observations. In the current analysis, the model consisted of the latent function f that depends on a vector of parameters that includes the description of treatment effect (Θ), a vector of patient specific covariates (X), and time (t) and the scaling function g, which was estimated as a constant (i.e., a scaling parameter) for each subject. The placebo response was modeled as additive or proportional to the latent variable. Step, exponential, or Bateman (biphasic) functions were tested to describe the temporal shape of the placebo effect. Different PK metrics, which were predicted using the individual PK parameters approach, were tested to drive the maximum inhibitory drug effect (I_{max}) model to describe the drug effect. An indirect response model was tested to describe the delay in the onset of the drug effect. Prior biologic use status singly or in combination with prior IL-17 inhibitor use status was explored as structural covariate on the concentration at 25% of maximum inhibition (IC_{25}) or I_{max}.

IIV was evaluated on all relevant parameters and was generally added in an exponential form for parameters which have a lower bound of zero and in an additive manner for parameters which can take on both negative and positive values. Box-cox transformation was considered for skewed IIV distribution. RUV was not relevant for PASI where the likelihood of the data was modeled in place of the data themselves.

The effects of covariates on parameters were tested in a similar manner as described for the population PK model and the tested relationships are listed in Table S2.

Exposure-response simulations

The population PK and PK/PD models were used to simulate exposure and response in patients with moderate-to-severe plaque psoriasis following administration of BI 730357 200 mg once daily, 400 mg once daily, and 200 mg twice daily under fed conditions. To maintain the correlation between covariates, individual vectors of covariates were sampled by using nonparametric bootstrap from study 1407-0030 in the analysis dataset. For each dosage regimen, 300 datasets, each containing 500 patients, were simulated. Only the point estimates of the parameters were used for simulations. Uncertainties in the parameter estimates and RUV were not considered.

In the PK simulations, the BI 730357 concentration-time profile of each patient was simulated for 15 days with steady-state presumably achieved at this time. The PK were simulated every 24 h for once daily dosing and every 12 h for twice daily dosing. In addition, rich PK samples were obtained after the last dose at day 15. To bridge PK to PD, the average concentration at steady-state was derived for each patient using the simulated individual clearance (CL) and bioavailability from the PK simulations, and then used to drive the drug effect in the PK/PD model. In the PD simulations, the inclusion criteria set forth in study 1407-0030 were accounted for, whereby only patients with baseline PASI score greater or equal to 12 were accepted. PASI was simulated at 0, 12, and 16 weeks after the first dose. The percentage of patients who achieved greater or equal to 50% (PASI50) and 75% (PASI75) reduction in PASI from baseline at week 12 and week 16 was derived for each simulated dataset and then summarized across all simulated datasets. For simulation of the BI 730357 exposure-PASI response relationship a vector of the average concentration at steady-state ranging from 0 to 8000 nmol/L by a 500 nmol/L increment was used for each simulated patient.

Data analysis

The analyses were performed using NONMEM version 7.4.4[17] installed on an Intel Xeon-based server running

Scientific Linux 6.3. NONMEM runs were performed using the gfortran compiler, version 7.5.0. Data management and further processing of NONMEM output were performed using R version 3.5.3.[18] Model estimations and simulations from the model were run using PsN version 4.8.1.[15,19] The R packages xpose4 version 4.6.1 and ggplot2 version 3.2.1 were used to generate plots for model evaluation.[20]

Parameter estimation was performed in NONMEM using the first-order conditional estimation method with interaction (FOCEI) method for the development of population PK model and the Monte Carlo importance sampling (IMP) for the development of the PK/PD model. The standard errors of the parameter estimates for PK model development were computed using MATRIX = S in the NONMEM $COVARIANCE record, but for the PK/PD model, which acknowledges a boundary to the data, rendering a more complex computation of the standard errors and necessitating a more accurate method, MATRIX = R was used. Model evaluation was based on the inspection of graphical diagnostics including goodness-of-fit plots and simulation-based diagnostics such as visual predictive checks (VPCs), prediction-corrected VPCs, and posterior predictive checks (PPCs) for the PASI end point.

RESULTS

Clinical data exploration

The population PK dataset from the four clinical studies included 109 healthy subjects and 244 patients with 7686 plasma samples measured for BI 730357 concentrations. The pooled population was 73.4% men and ages ranged from 18 to 75 years. The PK/PD dataset from study 1407-0030 included 274 patients with 1554 PASI observations. There were 69.3% of men and ages ranged from 18 to 75 years.

Patients generally had higher observed exposure compared with healthy subjects after administration of the same dose. BI 730357 absorption in patients appeared to be bi-phasic with the first peak at 2–4 h and the second peak at 12–24 h after the last dose. Graphical exploration of the trough concentrations observed in patients is shown in Figure 1. Increasing the dose from 200 mg once daily under fasted condition to 400 mg once daily and 200 mg twice daily under fed condition led to increased exposure, although the increase was observed to be sub-proportional with increasing dose. Approximate steady-state was reached at nominal visit day 15.

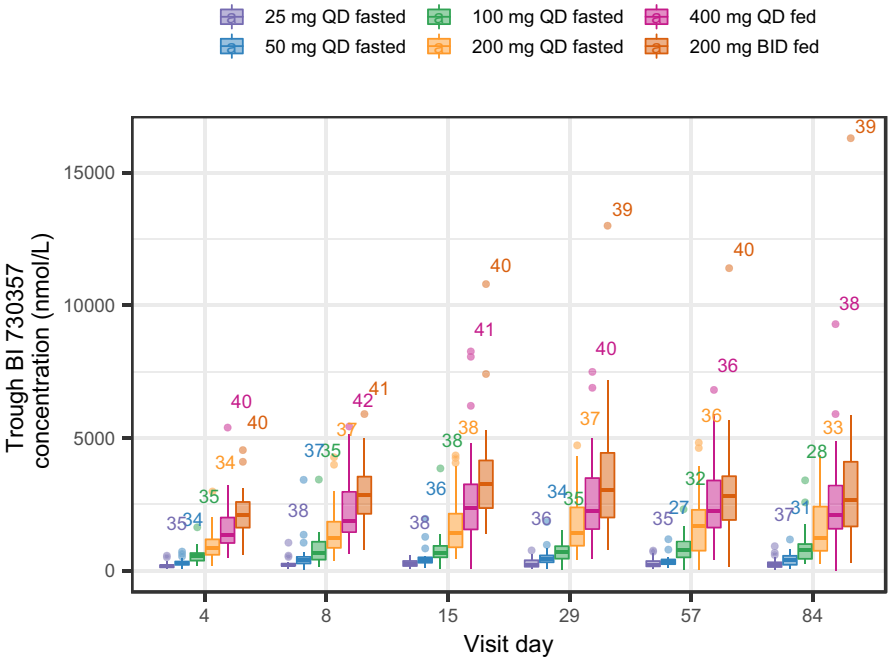

FIGURE 1 Observed trough plasma concentrations by visit for patients with moderate-to-severe plaque psoriasis in study 1407-0030 colored by dosage regimen. In the box plots, the middle line corresponds to the median, the upper and lower hinges correspond to the first and third quartiles (the 25th and 75th percentiles), the upper whisker extends from the hinge to the highest value that is within 1.5 IQR of the hinge, or distance between the first and third quartiles, the lower whisker extends from the hinge to the lowest value within 1.5 IQR of the hinge. Data beyond the end of the whiskers are plotted as points. The numbers indicate the number of observations per visit and dose group. BID, twice daily; IQR, interquartile range; QD, once daily.

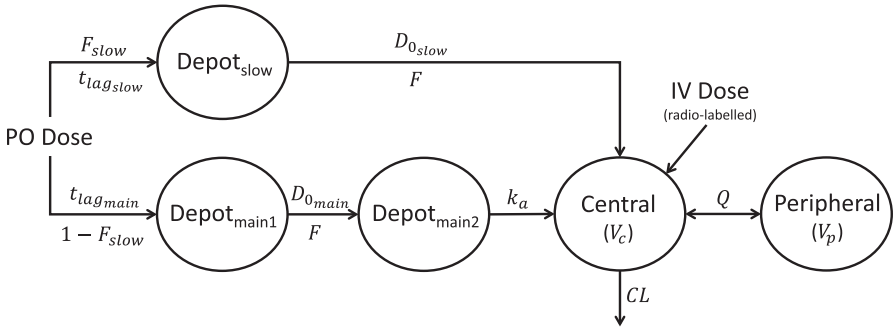

FIGURE 2 Schematic of the BI 730357 population pharmacokinetic model. Solid lines represent mass balance relationships and circles represent compartments. CL, clearance; D_{0main}, zero-order absorption duration for the main absorption path; D_{0slow}, zero-order absorption duration for the slow absorption path; F, bioavailability; F_{slow}, fraction absorbed via the slow absorption path; k_a, first-order absorption rate constant; Q, inter-compartmental clearance; $t_{lagmain}$, lag time of the main absorption path; $t_{lagslow}$, lag time of the slow absorption path; V_c, central volume of distribution; V_p, peripheral volume of distribution.

The percentage of patients who achieved PASI75 ranged from 25.0% to 32.4% in the dose groups 200 mg once daily, 400 mg once daily, and 200 mg twice daily, compared to 0% in the placebo group (Table S3). Despite the increase in dose, the percentage of patients who achieved PASI75 was similar among 200 mg once daily, 400 mg once daily, and 200 mg twice daily.

Population pharmacokinetic model

The population PK model consisted of a two-compartment model with dual absorption paths and a first-order elimination. Most of the dose was absorbed via a sequential zero-order and first-order process after a brief absorption lag and the remaining fraction of the dose was absorbed via a zero-order process after a long absorption lag. A schematic of the population PK model is shown in Figure 2, the parameter estimates are listed in Table 2, and the NONMEM model code and a dataset of one individual with mock DV records are provided in the Appendix S1.

The dose sub-proportional BI 730357 exposure was attributed to nonlinear absorption with respect to dose whereby the bioavailability decreased with increasing dose. Patients generally had lower bioavailability, slower decline in bioavailability with increasing dose, and lower CL compared with healthy subjects.

RUV was described by a combined error model with different variance of RUV specified for each unique combination of studies and diet status. In addition, IIV on RUV was specified and the additive RUV was scaled by using the lower limit of quantification of the different BI 730357 assays used in the studies.

The stepwise covariate model building procedure identified that higher baseline aspartate aminotransferase (AST) and C-reactive protein (CRP) were associated with lower CL. Higher CRP, typically observed in patients with moderate-to-severe plaque psoriasis, was associated with 21.4% lower CL compared to healthy subjects. After adjusting for these covariate differences, the CL in patients (5.19 L/h) was still lower than the CL in healthy subjects (6.72 L/h).

The model adequately described the data for each dosage regimen in study 1407-0030 as demonstrated by VPCs (Figures S1 and S2), although a trend for overprediction was noted at higher doses and longer times after first dose. Prediction-corrected VPCs also showed that data at study level were generally well-described (Figures S3 and S4). There was no evident model misspecification.

Population pharmacokinetic/pharmacodynamic model

A bounded integer model with improved numerical stability was estimated to describe PASI response to BI 730357. No typical placebo effects were identified but individual-level placebo effects were permitted along with delayed drug effects described by an indirect response model and an I_{max} function driven by the individual model-predicted average concentration at steady-state. Higher baseline sPGA was associated significantly with higher baseline PASI score. The parameter estimates are listed in Table 3 and the NONMEM model code is provided in the Appendix S1.

Because a drug effect plateau was observed at high doses, estimation of I_{max} was attempted (I_{max} = 0.562), leading to significant improvement in model fit compared to when I_{max} was fixed to one. IIV on I_{max} was explored and carried forward along with effects of prior biologic and prior IL-17 inhibitor use as structural covariates.

TABLE 2 Parameter estimates of the BI 730357 population pharmacokinetic model.

Parameter	Estimate	RSE (%)
F for study 1407-0030	0.553	7.48
F for study 1407-0002	0.652	7.65
F for study 1407-0032	0.429	9.58
F for study 1407-0033	0.487	19.4
Additive shift of fed state on F[a]	0.586	34.7
Slope for dose effect on F for fasted healthy subjects[a] (1/mg)	−0.00618	16.9
Slope for dose effect on F for fed healthy subjects[a] (1/mg)	−0.00514	19.6
Slope for dose effect on F for fasted patients[a] (1/mg)	−0.00517	14.5
$t_{lagmain}$ (h)	0.167	fixed
D_{0main} (h)	0.538	8.12
Multiplier for fed state on D_{0main}	3.52	41.7
Power for dose effect on D_{0main}	−0.591	37.7
k_a (1/h)	0.203	6.00
Multiplier for fed state on k_a	1.25	7.49
F_{slow}	0.218	8.83
Additive shift of study 1407-0033 on F_{slow}[a]	−0.850	63.3
$t_{lagslow}$ (h)	11.5	1.33
D_{0slow} (h)	17.9	2.07
CL (L/h)	6.72	8.44
Multiplier for patients on CL	0.773	8.55
Q (L/h)	23.1	6.82
V_c (L)	19.5	9.43
V_p (L)	169	6.53
Allometric exponent for CL and Q[b]	0.750	fixed
Allometric exponent for V_c and V_p[b]	1.00	fixed
Additive shift of iCF on F[a]	0.287	5.81
Additive shift of twice daily dosing on F[a]	−0.448	38.5
Proportional shift of iCF on k_a	0.391	7.01
Proportional shift of study 1407-0032 on k_a	0.575	22.5
Exponent of CRP on CL[c]	−0.120	19.8
Exponent of AST on CL[c]	−0.232	26.4
Multiplier for C_{trough} on residual unexplained variability	1.27	1.60
Interindividual variability[d]		
F	0.420	11.4
D_{0main} (CV)	0.760	6.36
k_a (CV)	0.285	11.1
F_{slow}	0.774	10.3
CL (CV)	0.417	4.09
V_c (CV)	0.739	6.20
Proportional residual unexplained variability (CV)	0.408	5.05
Residual unexplained variability[c]		
Proportional, i.v., healthy subjects (CV)	0.377	26.2
Additive, i.v., healthy subjects (nmol/L)	0.0316	fixed
Proportional, oral, fasted, healthy subjects (CV)	0.134	6.49
Additive, oral, fasted, healthy subjects (nmol/L)	2.03	4.95
Proportional, oral, fasted, patients (CV)	0.203	3.89
Additive, oral, fasted, patients	5.34	3.26
Proportional, oral, fed, healthy subjects and patients (CV)	0.173	5.33
Additive, oral, fed, healthy subjects and patients (nmol/L)	2.84	7.23

Abbreviations: AST, aspartate aminotransferase; CL, clearance; CRP, C-reactive protein; C_{trough}, trough concentration; CV, coefficient of variation; D_{0main}, zero-order absorption duration for the main absorption path; D_{0slow}, zero-order absorption duration for the slow absorption path; F, bioavailability; F_{slow}, fraction absorbed via the slow absorption path; iCF, intended commercial formulation; i.v., intravenous; k_a, first-order absorption rate constant; PK, pharmacokinetic; Q, intercompartmental clearance; RSE, relative standard error; $t_{lagmain}$, lag time of the main absorption path; $t_{lagslow}$, lag time of the slow absorption path; V_c, central volume of distribution; V_p, peripheral volume of distribution.

[a]On logit scale.

[b]Weight was centered on 70 kg.

[c]Centered on the median in healthy subjects.

[d]Interindividual variability and residual unexplained variability are reported in the SD scale. The SD approximates the CV of interindividual variability for log-normally distributed individual parameters.

The model predicted individual data well (data not shown) and adequately described the relative change from baseline PASI for each dose level in study 1407-0030, as shown by VPC (Figure S5). PASI75 at 12 weeks after first dose was also well-described, as demonstrated by PPC (Figure S6). The Pearson residuals showed good model performance (Figure S7).

Based on the VPC for PASI score (Figure S8), the model overpredicted the median observed data in the placebo group and this is partly attributed to the PASI score at baseline for the placebo group being low relative to other dose groups. In addition, the model also overpredicted the variability in the longitudinal PASI score in the placebo group. The PK/PD model described the longitudinal

TABLE 3 Parameter estimates of the population pharmacokinetic/pharmacodynamic model.

Parameter	Estimate	RSE (%)
Scaling parameter	0.0981	4.87
Baseline	−0.780	1.81
Box-Cox coefficient for baseline	3.03	6.51
Maximum placebo response	0	fixed
I_{max} for no prior biologic use	0.411	13.4
I_{max} for prior non-IL-17 inhibitor use	0.284	21.6
I_{max} for prior IL-17 inhibitor use	0.186	30.6
IC_{50} (nmol/L)	490	18.0
γ	1.00	fixed
Half-life to reach I_{max} (days)	33.8	5.65
Baseline sPGA effect on baseline	0.154	20.2
IIV[a]		
Scaling parameter (CV)	0.629	7.23
Baseline	0.176	7.13
Maximum placebo response	0.236	9.80
I_{max}	1.82	10.4
Correlation between IIV I_{max} and scaling parameter	0.709	9.26

Abbreviations: γ, sigmoidicity factor in the maximum effect model; CV, coefficient of variation; IC_{50}, concentration at half maximum inhibition; I_{max}, maximum inhibitory drug effect; IIV, interindividual variability; RSE, relative standard error; sPGA, static physician global assessment.

[a]Interindividual variability are reported in the SD scale. The SD approximates the CV of interindividual variability for log-normally distributed individual parameters.

PASI score adequately for each active dosage regimen and no other model misspecification was evident.

Simulated Psoriasis Area and Severity Index outcome

The population PK model was used to simulate the average concentration at steady-state following administration of BI 730357 200 mg once daily, 400 mg once daily, and 200 mg twice daily under fed condition. These exposures were used with the PK/PD model to simulate PASI response.

The simulated percentage of patients attaining less than PASI50, PASI50, and PASI75 at 12 and 16 weeks after first dose are presented by dosage regimen (Figure 3a). The percentage of patients attaining PASI75 at week 12 are similar (median range 23%–26.4%) between the dosing regimens 200 mg once daily, 400 mg once daily, and 200 mg twice daily with largely overlapping 95% confidence interval. There was a marginal increase in the percentage of patients attaining PASI75 at week 16 (median range 27.2%–30.9%), suggesting a plateau in longitudinal PASI75 response.

The simulated effect of prior biologic use on percentage of patients attaining less than PASI50, PASI50, and PASI75 at 12 weeks after first dose are presented by dosage regimen (Figure 3b). Patients with no prior biologic use had the highest percentage of PASI75, followed by patients with prior non-IL-17 inhibitor use, and then patients with prior IL-17 inhibitor use. The highest simulated PASI75 response (median 32.0%) was seen in patients without prior biological use that were administered 200 mg twice daily.

The simulated BI 730357 exposure-PASI response relationship is shown in Figure 4. Maximum BI 730357 effect of about 50% relative change from baseline PASI score at week 12 was reached at steady-state average concentration of about 2000 nmol/L. An increase in the steady-state average concentration to above 2000 nmol/L was predicted to result in minor improvements of the PASI response, indicating an exposure-response plateau.

DISCUSSION

In this study, we characterized BI 730357 PK properties following oral administration and investigated the relationship between exposure and PASI response using data pooled from 109 healthy subjects and 274 patients with moderate-to-severe plaque psoriasis. Application of the PK/PD model predicted an exposure-response plateau in PASI outcomes for BI 730357 exposure above 2000 nmol/L.

The PK of BI 730357 in healthy subjects and patients with moderate-to-severe plaque psoriasis was adequately characterized by a two-compartment model with dual absorption paths and a first-order elimination. The parallel slow absorption path with an estimated 12 to 30 h delay may be related to colonic absorption. Given the late second concentration peak observed at 12–30 h after dose, the time course does not support the possibility of enterohepatic recycling, and colonic absorption may be more likely. BI 730357 has low water solubility,[21] and physiological based,[22] as well as compartmental[23] PK modeling of orally administered compounds with poor solubility has identified the sigmoid colon[22] and the intestine[23] as segments likely responsible for solubility-limited late absorption.

A study effect was found on various absorption parameters. Although these relationships were seemingly empirical, they may be driven by differences between the conduct of these studies in terms of study phase, inpatient setting or not, study duration, study population other than explained by other covariates, meal type etc., which may in turn be associated with differentiated compliance patterns to the prescribed dosing regimen and diet status that impact the absorption of BI 730357.

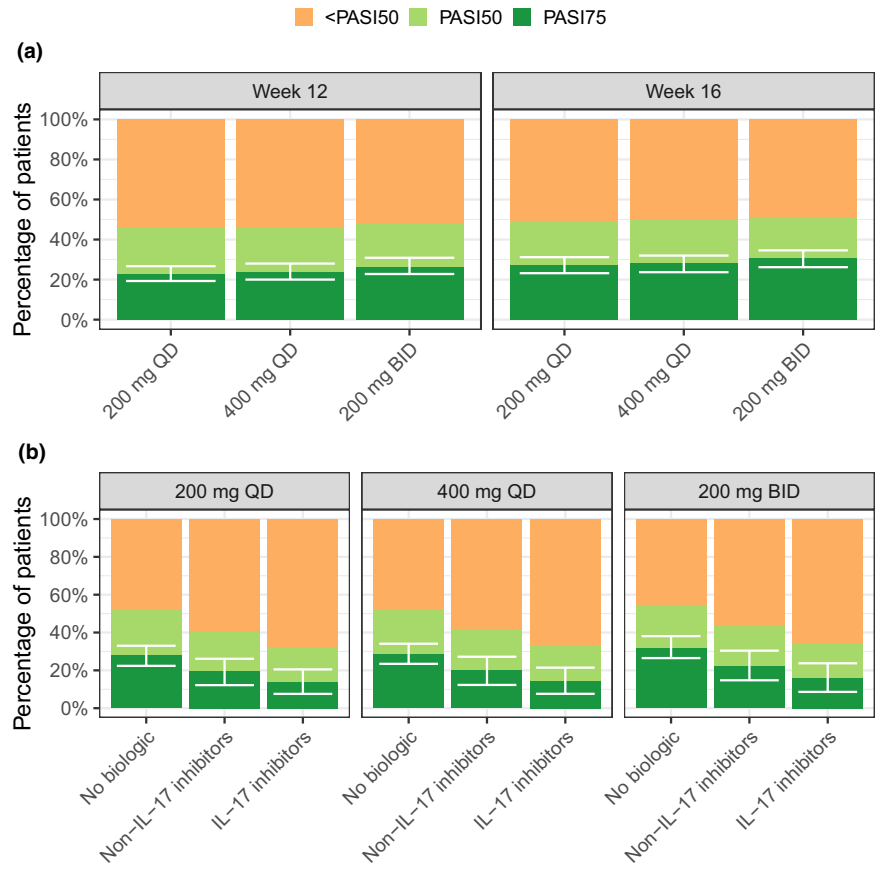

FIGURE 3 Simulated percentage of patients with moderate-to-severe plaque psoriasis attaining less than PASI50, PASI50, and PASI75. (a) At 12 and 16 weeks after the first dose by dosage regimen and (b) by dosage regimen and prior biologic use at 12 weeks after the first dose. The white error bar indicates the 95% confidence interval of the percentage of patients attaining PASI75. BID, twice daily; PASI, Psoriasis Area and Severity Index; QD, once daily. <PASI50, less than 50% reduction in PASI from baseline; PASI50, greater or equal to 50% and less than 75% reduction in PASI from baseline; PASI75, greater or equal to 75% reduction in PASI from baseline.

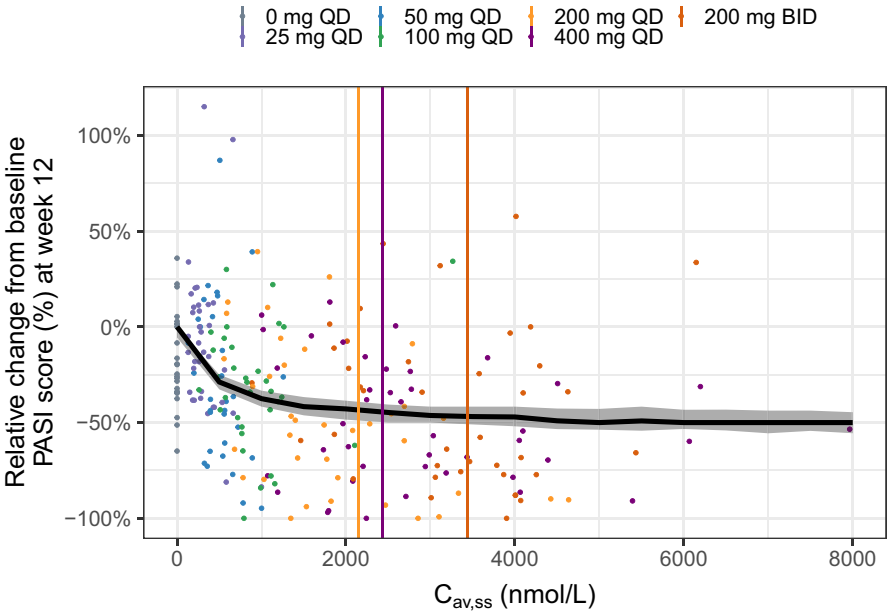

FIGURE 4 Simulated BI 730357 exposure-PASI response relationship at 12 weeks after the first dose. The black line represents the simulated median relative change from baseline PASI score, and the gray shaded ribbon represents the associated 95% confidence interval. The vertical lines indicate simulated median average concentrations at steady state colored by dosage regimen. The dots are the observed data colored by dosage regimen. BID, twice daily; $C_{av,ss}$, average concentration at steady state; PASI, Psoriasis Area and Severity Index; QD, once daily.

Baseline sPGA was found to be positively correlated with baseline PASI score. The identified relationship was statistically significant and plausible because PASI and sPGA are both scores used to assess plaque psoriasis patients' disease severity with respect to induration, erythema, and scaling. Inclusion of baseline sPGA as a predictor for baseline PASI score in the model reduced the individual unexplained variability at baseline in the observed data and allowed simulations of baseline PASI score that were less variable and more realistic given specific baseline sPGA score.

The identification of the association between elevated CRP and reduced CL supports the notion suggested by previous studies that expression of drug metabolizing

enzyme may be downregulated in patients with inflammatory diseases compared to healthy subjects.[24–26] The described CRP effect on CL is also consistent with previous findings that inflammatory biomarkers may be predictive of PK differences between healthy subjects and patients with inflammatory diseases.[27,28] Still, the CRP effect on CL could not fully explain the impact of moderate-to-severe plaque psoriasis on BI 730357 PK. Higher body weight and lower AST were also identified to be significantly associated with higher CL. In addition to these covariate effects, a patient effect on CL was identified. On average, the CL in patients was 22.7% less than the CL in healthy subject after adjusting for differences in covariate values.

The analyses were associated with some limitations. An empirical twice daily dosing effect on F was introduced to the population PK model. Whereas the twice daily dosing effect on F lacked mechanistic interpretation, it improved the description of the longitudinal trough concentrations for 200 mg twice daily and it was fit for the purpose of simulating 200 mg twice daily without extrapolation to higher doses or alternative conditions. The estimated study 1407-0033 effect on F_{slow} was uncertain (relative standard error 64.4%). Its inclusion allowed better description of study 1407-0033 data, but the parameter was not used for simulation and hence the uncertainty did not impact the predicted BI 730357 exposure used to simulate PASI response. Finally, successful minimization was not attained during population PK model development and finalization. Despite these limitations, the population PK model appeared otherwise stable with a low condition number and successful termination of the $COVARIANCE step in NONMEM. The parameters were generally precisely estimated, and the model provided a good description of PK data. The ability to characterize the variety in data from administration in healthy subjects and patients, once daily and twice daily, using oral and intravenous routes, renders credibility to the population PK model.

A bounded integer PK/PD model with improved numerical stability successfully characterized the BI 730357 effect on the observed PASI in patients with moderate-to-severe plaque psoriasis. Advantages attached to the use of bounded integer models in modeling PASI data include accounting for scale boundaries (i.e., PASI ranges from 0 to 72), simulation according to the boundaries, and parsimony in terms of the number of parameters to be estimated. The bounded integer model forces an integer nature of the predicted PASI data within the scale boundaries while the observed PASI score can take on certain non-integer values. The bounded integer model was nevertheless deemed fit for purpose considering that the decimal values are trivial relative to the overall scale of the measurement. Consistent with previous findings,[12] no changes in model fit were observed after implementation with improved numerical stability using the non-gradient-based IMP estimation method. However, the improved numerical stability implementation appeared to result in faster run time. Further improvement in run time could be expected if the Laplace estimation method had been used, but it was not attempted as the estimation time was already fast.

The PK/PD model slightly overpredicted the median observed PASI in the placebo group and the variability in longitudinal PASI in the placebo group, whereas the active treatment groups were well-described. Various placebo effect models were tested but did not provide a significantly better fit than fixing the typical placebo effect to zero. Individual-level placebo effects were still necessary for an adequate description of the data, pointing toward psoriasis being a condition with highly variable, less predictable disease progression.

However, the PK/PD model predicted the relative change from baseline well, based on the VPC, and predicted the percentage of PASI75 well, based on the PPC. The model was deemed fit for the purpose of simulating PASI outcomes for BI 730357 dosage regimens, as it described both the percentage of PASI75 and the longitudinal PASI score adequately for the active treatment groups.

In the final PK/PD model, the drug effect on PASI was driven by the steady-state average concentration. With the PK steady-state assumption, the PK turnover was assumed to be negligible and any delay in PD observed was attributed solely to PD turnover, potentially resulting in a biased PD half-life estimate. However, we believe that the PASI half-life estimated in the current analysis should be invariant to the PK steady-state assumption given that the turnover of PASI with a half-life in the range of weeks (~5 weeks) is much slower than the turnover of the BI 730357 PK with a half-life in the range of hours (~3 h) for patients with psoriasis. Indeed, when different PK exposure metrics, including both time-varying and steady-state exposure, were tested, almost identical model fit and PASI half-life estimates were found. On this basis, the reported model should have similar mechanistic interpretation and simulation properties as alternative models with drug effects driven by time-varying PK exposure metrics.

Our analyses described some subproportional relationships. Observed trough concentrations in patients (Figure 1) showed that increasing the dose from 200 mg once daily to 400 mg once daily and 200 mg twice daily led to increased exposure although the observed increase was subproportional with increasing dose. Indeed, an inverse relationship between dose and F was identified as significant. The simulated exposure-response relationship (Figure 4) described a plateau where increased steady-state average concentration above 2000 nmol/L resulted in marginal improvement in the relative change from baseline PASI score. The PASI simulations also predicted

a plateau in longitudinal response (Figure 3a). There was a marginal increase in the percentage of patients attaining PASI75 from 12 to 16 weeks after the first dose. Therefore, longer treatment duration or higher dose beyond the dosage regimens in the analyzed clinical data is unlikely to result in improved PASI outcomes.

In summary, the population PK and the PK/PD models were helpful to predict the impact of BI 730357 dosing regimens on the PASI response. Robust outcome predictions were enabled by simulation using replicates of a mimicked phase III study design with each dosing regimen containing a large patient population. Inclusion of a broad range of dosing regimens allowed characterization of the full exposure-response profile to answer key questions, such as if a higher exposure would lead to a higher efficacy. Our analyses demonstrated how application of a bounded integer model resulted in accurate, parsimonious description, and simulations of composite data with score boundaries, and ultimately contributed to model-informed drug development.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript and designed the research. Q.X.O., A.K., and E.L.P. performed the research. Q.X.O., A.K., and E.P. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

Q.X.O., A.K., and E.P. are employees of Pharmetheus AB and E.L.P. holds stock in the company. J.K. and M.F. are employees of Boehringer Ingelheim Pharmaceuticals, Inc. and B.W. is an employee of Boehringer Ingelheim Pharma GmbH & Co. KG. Support from Q.X.O., A.K., and E.P. at Pharmetheus was contracted and funded by Boehringer Ingelheim.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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